Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof

Post-Infectious COVID-19-Associated Hyperinflammatory Syndrome in an Older Patient

Giuseppe Famularo MD PhD , Barbara De Pascalis MD , Nicoletta Di Lallo MD , Silvia Raja MD , Anna Linda Patti MD

PII: S0002-9629(21)00368-2
DOI: https://doi.org/10.1016/j.amjms.2021.10.007
Reference: AMJMS 1499

To appear in: *The American Journal of the Medical Sciences*

Received date: 20 March 2021
Accepted date: 15 October 2021

Please cite this article as: Giuseppe Famularo MD PhD , Barbara De Pascalis MD , Nicoletta Di Lallo MD , Silvia Raja MD , Anna Linda Patti MD , Post-Infectious COVID-19-Associated Hyperinflammatory Syndrome in an Older Patient, *The American Journal of the Medical Sciences* (2021), doi: https://doi.org/10.1016/j.amjms.2021.10.007

Post-Infectious COVID-19-Associated Hyperinflammatory Syndrome in an Older Patient

Giuseppe Famularo MD PhD, Barbara De Pascalis MD, Nicoletta Di Lallo MD, Silvia Raja MD,

Anna Linda Patti MD

Internal Medicine, San Camillo Hospital, Rome, Italy

Short Title: COVID-19 Hyperinflammatory Syndrome

Corresponding author at: Dr. Giuseppe Famularo, Internal Medicine, San Camillo Hospital, Circonvallazione Gianicolense, 00152 Rome, Italy; (E-mail: gfamularo@scamilloforlanini.rm.it)

Key Words: COVID-19, SARS-CoV-2, multisystem hyperinflammatory syndrome

Dear Editor:

A multisystem hyperinflammatory syndrome has been described in children with COVID-19, however there are no reports among older adults.[1-4]

A 70-year-old Caucasian man presented in November 2020 during the second wave of the pandemic with a 2-week history of worsening conjunctivitis, polyarthritis, diffuse myalgia, and a skin rash.

The patient had been admitted to another hospital 6 weeks earlier because of COVID-19 pneumonia. At the time, the diagnosis was confirmed by both a reverse transcription-polymerase chain reaction (RT-PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on a nasopharyngeal swab with a cycle threshold value 25 (<37 defined as a positive test result) and typical findings on a total-body contrast-enhanced computed tomography (CT) that showed ground-glass patchy opacities in both lungs, no thromboembolism, and an incidental left renal cancer. D-dimer fluctuated between 1,100 and 1,600 ng/mL (<500 ng/mL) and search for *Mycoplasma* and other respiratory pathogens was negative. Dexamethasone, low-dose enoxaparin, and azithromycin were administered, the clinical course was uneventful, there was no need of respiratory support or evidence of other organ dysfunction, and arthritis and skin manifestations were not recognized. At discharge, dexamethasone, and enoxaparin, and azithromycin were discontinued, RT-PCR testing for SARS-CoV-2 was negative, and D-dimer had returned to within the normal range.

The patient's previous medical history was unremarkable, he was not taking any

medications and denied the use of over-the-counter and illicit substances. There was no personal or family history of rheumatic, autoimmune, dermatologic, or allergic diseases.

At admission, the patient was febrile (39.2 °C) with normal vital signs. Physical examination was notable for bilateral, non-exudative conjunctival injection, periorbital edema with overlying erythema, erythroderma over the face, and a rash over the trunk, consisting of erythematous round-shaped macules, raised papules, and plaques 1-3 cm in diameter (Figure). The joints of the hands, wrists, knees, and ankles were symmetrically swollen and tender with a limited range of motion. The joint pain was 9/10 intensity on a visual analogue scale and worsened with palpation and movements.

The white cell count was 15,000/mm^3, with lymphocytes of 1,200/mm^3, C-reactive protein (CRP) level was of 40 mg/L, ferritin was 900 ug/L (normal 30-250 ug/L), D-dimer 1,500 ng/ml (normal 250-500 ng/ml), and fibrinogen 7 g/L (normal 2.5-5.0 g/L). Liver and kidney function tests and blood levels of complement, Ig E, and uric acid were normal. Extensive evaluation for infectious causes was pursued. RT-PCR testing for SARS-CoV-2 was negative, blood cultures grew no pathogens and procalcitonin was normal. Serologies for rickettsial diseases, *Borrelia*, syphilis, HIV-1 and HIV-2, *Adenovirus*, *Parvovirus*, *Coxsachie* and *Echo* virus, measles, and hepatitis B and C were negative. Search for autoimmunity including antinuclear antibodies, anti-dsDNA antibodies, rheumatoid factor, cyclic citrullinated peptide antibody, and antineutrophil cytoplasmic antibodies was also negative. Anti-SARS-CoV-2 antibodies were not measured and HLA-B27 was not tested. Blood levels of troponins and B-type natriuretic peptide were normal; echocardiography showed a normal left ventricular ejection fraction and no other abnormalities. Findings of a contrast-enhanced total-body CT disclosed no signs of COVID-19 pneumonia and no other abnormalities

except the 2 x 3 cm mass of the left kidney.

We started corticosteroids, 1 week later the patient reported improvement of his symptoms and he was apyrexial on the 15th day. Conjunctivitis, polyarthritis, joint swelling, erythroderma, and the skin rash over the trunk had disappeared nor he was complaining of polyarthralgia or myalgia. Corticosteroids were progressively tapered and suspended. At follow-up 3 months later, the patient was doing well with normal blood levels of CRP, D-dimer, and ferritin. At that time, he had not received a SARS-CoV-2 vaccine.

The clinical presentation of this patient involved fever, polyarthritis, myalgia, mucosal, and dermatologic findings with onset of symptoms several weeks later after confirmed COVID-19 pneumonia. Polyarthritis, conjunctivitis, erythroderma, and other skin manifestations were the key clinical features. Other systems were not involved, in particular there was no kidney, liver or myocardial dysfunction. SARS-CoV-2 shedding was not found. He was treated with corticosteroids and recovered.

On consideration of the patient's history, clinical findings and the timing of onset we diagnosed a post-infectious hyperinflammatory syndrome related to COVID-19. We ruled out autoimmunity and other infections and inflammatory disorders. Furthermore, many points argue against a paraneoplastic syndrome. The renal cancer was an incidental finding, there were no metastases, and no flare-up of fever or other clinical signs and symptoms of systemic or organ-specific inflammation occurred after corticosteroids were suspended.

A multisystem hyperinflammatory syndrome resembling Kawasaki disease, toxic shock

syndrome, and macrophage activation syndrome is a recognized entity that has been associated with COVID-19 in children, adolescents, and young adults.[1-4] In addition to the older age, our case is unique in the total absence of cardiac manifestations as almost all patients have left ventricular dysfunction and myocarditis.[5] The clinical course of the syndrome may vary widely and in severe cases patients may progress to multiorgan failure.[1-4] Active SARS-CoV-2 replication and shedding are rarely found at the time of presentation.[1-4] This suggests a secondary or no direct role at play for the virus in the pathophysiology of the syndrome. Immune dysregulation, which might be antibody, immune complex or cytokine mediated, and SARS-CoV-2-related endothelitis are probably implicated.[6,7] Other unknown mediators and host factors can be involved.

Even though older adults are most affected by the COVID-19 pandemic the post-infectious hyperinflammatory syndrome is highly unusual among older patients with COVID-19. This is an important point and the underlying reasons for this discrepancy between older and younger patients with COVID-19 are unclear. As a matter of fact, the clinical features of our patient, the elevated markers of inflammation and thrombosis, and the exclusion of other obvious infectious and inflammatory disorders shared a striking resemblance to previously reported cases of post-COVID-19 multisystem hyperinflammatory syndrome in children, adolescents, and younger subjects.[1-4]

Our report heightens awareness of the possibility of delayed post-infectious COVID-19-associated hyperinflammatory disorders in older adults. The long-term outcome of these cases is unknown and evidence for the best treatment remains scant.

Conflict of interests

The authors have no actual or potential conflicts of interest.

References

1. **Verdoni L, Mazza A, Gervasoni A, et al.** An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet.* 2020;395: 1771-1778
2. **Dufort EM, Koumans EH, Chow EJ, et al**. Multisystem inflammatory syndrome in children in New York state. N Engl J Med. 2020;383: 347-358.
3. **Jiang L, Tang K, Irfan O, et al.** COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20: e276-288.
4. **Morris SB, Schwartz NG, Patel P, et al.** Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection – United Kingdom and United States, March-August 2020. MMWR. 2020;69: 1450-1456.
5. **Hékimian G, Kerneis M, Zeitouni M, et al.** Coronavirus Disease 2019 acute myocarditis and multisystem inflammatory syndrome in adult intensive and cardiac care units. Chest. 2021;159: 657-662.
6. **Consiglio CR, Cotugno N, Sardh F, et al.** The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020;183: 968-981.
7. **Ackermann M, Verleden SE, Kuehnel M, et al.** Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383: 120-128.

Figure Legend

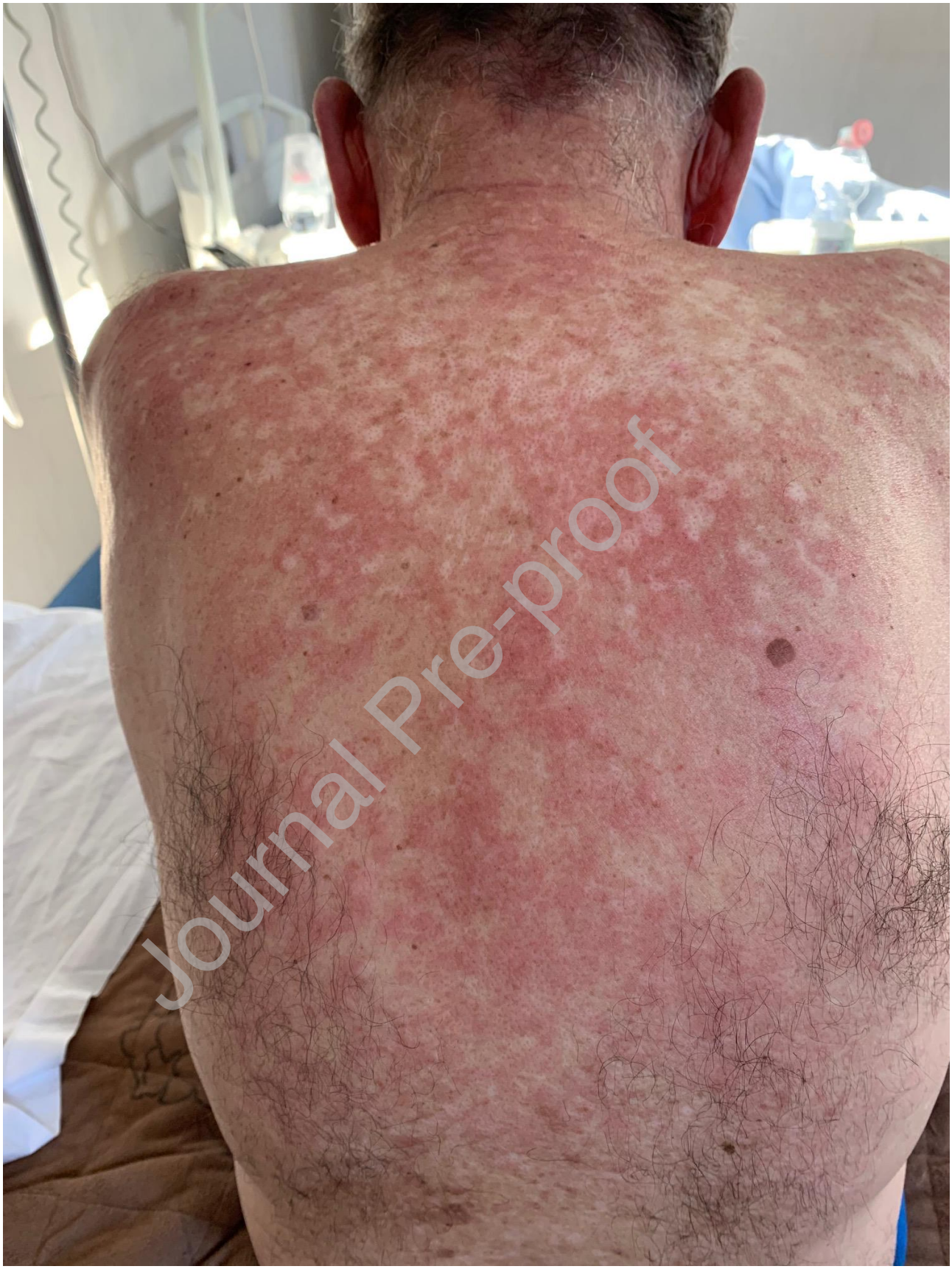

Figure 1. Rash over the trunk, consisting of erythematous round-shaped macules, raised papules, and plaques over the trunk.

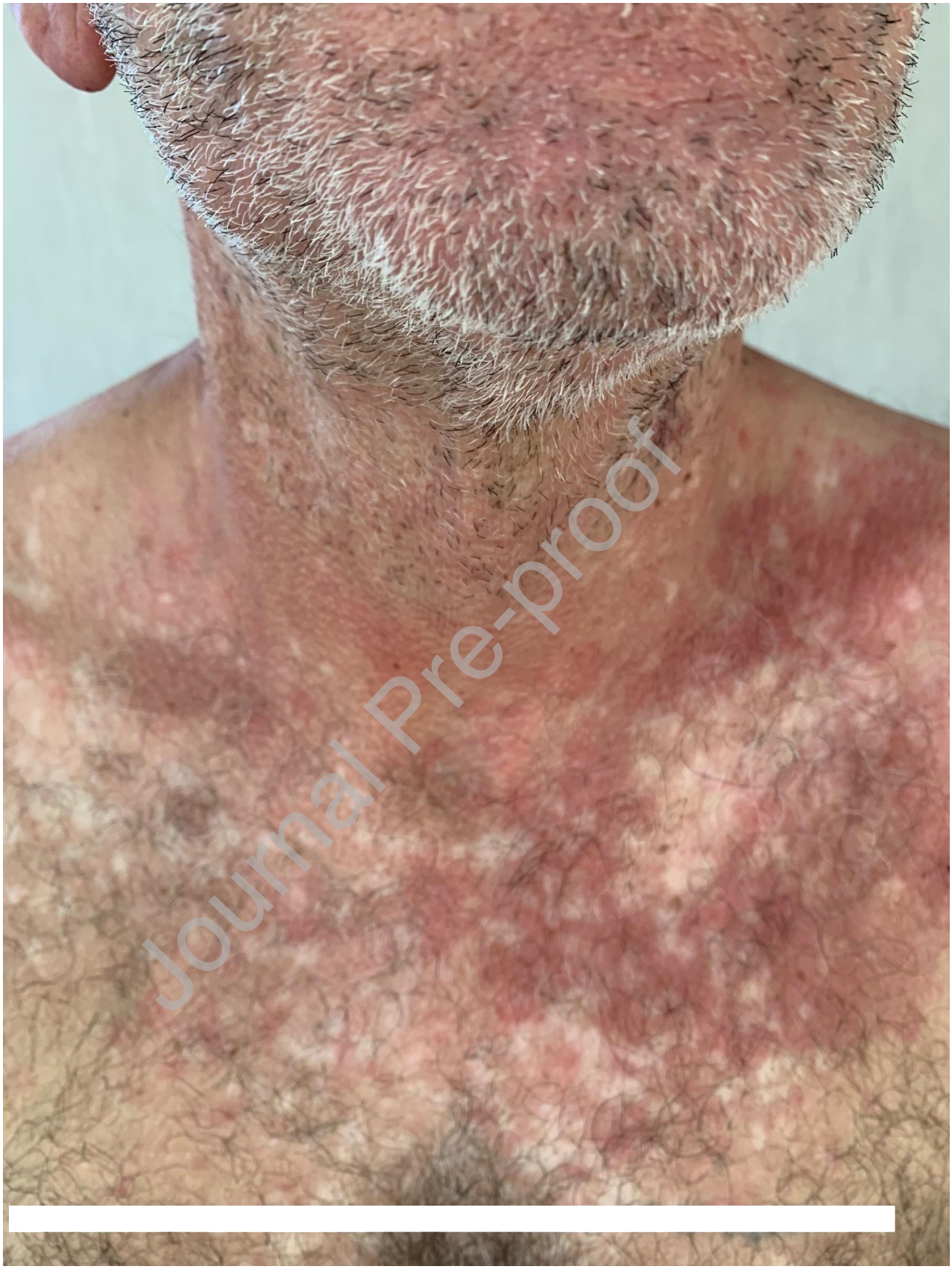

Figure 2. Rash over the trunk, consisting of erythematous round-shaped macules, raised papules, and plaques over the neck.